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New therapeutic choices for infections caused by methicillin-resistant *Staphylococcus aureus*

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Abstract

In recent years, a marked increase in the incidence of infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA) has occurred in many countries. This review addresses the effectiveness and limitations of drugs classically used for the treatment of MRSA, e.g. vancomycin, and also newer anti-MRSA antimicrobials, e.g. second-generation glycolipopeptides, tigecycline, and β-lactams.

Keywords: MRSA, treatment, gram positives, linzolid, vanomycin, daptomycin, tigecycline, ceftobiprole, ceftarole, review
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Alternatives to Classically Used Drugs

Vancomycin

Vancomycin has been, and still is, the mainstay of therapy for methicillin-resistant *Staphylococcus aureus* (MRSA) infections for more than 50 years, but treatment failures are frequently reported [1–6]. Vancomycin has worse clinical results than β-lactam drugs in treating infections caused by strains susceptible to both [2,3,5,7,8]. The intrinsic limitations of vancomycin include poor tissue penetration, particularly in the lung, relatively slow bacterial killing, and toxicity.

Fully vancomycin-resistant strains (vancomycin-resistant *S. aureus* (VRSA)) remain rare. These strains have so far had limited clinical consequences, not having been associated with invasive disease [9–11]. They have been isolated mainly in patients simultaneously infected by, or colonized with, MRSA and vancomycin-resistant enterococci.

Vancomycin-intermediate *S. aureus* (VISA) strains were initially reported from Japan by Hiramatsu *et al.* in 1996 [12]. VISA strains, defined by an MIC of vancomycin of 4–8 mg/L, represent less than 1% of all *S. aureus* strains isolated throughout the world. These isolates are murein hyperproducers. Owing to the limited tissue penetration of vancomycin, patients infected with these strains have a poor response to this drug. When only a proportion of a strain of *S. aureus* is vancomycin-intermediate, the strain is called 'hetero-VISA'. Hetero-VISA isolates are more common than VISA isolates, and are purportedly more difficult to treat than fully susceptible isolates [5,13].

There is growing concern that vancomycin is losing activity for MRSA infections. So-called 'vancomycin creep' is defined as a progressive increase in the MICs for isolates of *S. aureus*, with strains remaining susceptible but at the high end of the CLSI susceptibility range [14]. This creep has been observed in some [1,15–18], but not all [19,20], institutions.

In 2006, vancomycin MIC breakpoints for *S. aureus* were lowered, resulting in an increase in the proportion of strains considered to be resistant (Table 1). This decision reflected a growing amount of microbiological and clinical data indicating that isolates of *S. aureus* are less likely to respond to vancomycin therapy when MICs are >1 mg/L [16,21]. For example, Soriano *et al.* from Spain reported increased mortality associated with MRSA bacteraemia when vancomycin was empirically used for the treatment of infection due to strains with a vancomycin MIC >1 mg/L [22]. Although there is disagreement on the best laboratory method with which to determine the *in vitro* susceptibility of these isolates, microbiology laboratories should report numerical MICs for isolates of *S. aureus* obtained from clinically significant infections.

Patients with infections caused by strains with a vancomycin MIC >1 mg/L can be managed by the combination of vancomycin with other drugs or by doses of vancomycin high enough to achieve troughs >15 mg/L[23]. However, the risk of higher dosages is an increase in nephrotoxicity.

One alternative approach is to administer vancomycin with rifampin [24], a common clinical practice in many institutions. However, the *in vitro* data regarding the superiority of this combination are contradictory [25–27], and

TABLE 1. Old and new breakpoints of *Staphylococcus aureus* for vancomycin susceptibility

	Susceptible (mg/L)	Intermediate (mg/L)	Resistant (mg/L)
Old	≤4	8–16	≥32
New	≤2	4–8	≥16

information from animal models [28,29] or humans is insufficient for us to conclude that adding rifampin to vancomycin for the treatment of MRSA isolates is always superior to the administration of vancomycin alone [24,30,31]. Some results suggest that the potential for hepatotoxicity, drug–drug interactions, and the emergence of resistant *S. aureus* isolates warrants a careful risk–benefit assessment before rifampin is added to standard antimicrobial treatment for severe *S. aureus* infections [32,33].

Using a different approach, models have suggested that a single dose or a very short course of gentamicin added to vancomycin may maximize synergistic and bactericidal activity and minimize toxicity in therapy for isolates of *S. aureus* with a gentamicin MIC of <500 mg/L, but not for highly gentamicin-resistant isolates [34–38]. A combination of vancomycin and gentamicin should be used carefully in patients with MRSA infections, and only for a very short period of time, to avoid nephrotoxicity [39–46].

Linezolid

Linezolid is the first of the oxazolidinones, a new class of antimicrobial agents. Linezolid inhibits protein synthesis at the ribosome level, and may have a bactericidal or bacteriostatic effect, depending on the circumstances [47–50].

Linezolid is active *in vitro* against most Gram-positive bacteria, including methicillin-susceptible *S. aureus* (MSSA) and MRSA [51–54]. There have been anecdotal reports of resistance of MRSA to linezolid [55–61].

Linezolid is highly bioavailable after oral administration (more than 90%), and can be administered intravenously [62]. The volume of distribution is approximately 20 L, protein binding is 31%, and the half-life is 6 h. Linezolid is largely metabolized in the liver, and 30% of the drug is eliminated unchanged in the urine. Linezolid requires no dosing adjustments in cases of either renal or hepatic failure [63–71].

Linezolid is generally well tolerated, but myelotoxicity and neurotoxicity are the major adverse events. Myelotoxicity is mainly expressed as thrombocytopenia in patients with more than 14 days of treatment, predominantly occurring in individuals with pre-existing myelosuppression or receiving drugs that are also myelotoxic. Lactic acidosis, peripheral neuropathy, and optic neuropathy are very uncommon but potentially irreversible adverse consequences of linezolid use. These complications may occur in patients with long-term use of the drug, and its use is therefore presently restricted to a maximum of 4 weeks [72–78].

Linezolid has been approved for the treatment of community and nosocomially acquired pneumonia and skin and soft tissue infections (SSTIs). The clinical trials included cases caused by MRSA. Information regarding the use of linezolid in the treatment of bacteraemia, catheter-related bloodstream infections (CR-BSIs) and infective endocarditis (IE) is limited [79–82].

Linezolid is probably the drug of choice for the treatment of patients with ventilator-associated pneumonia (VAP) caused by MRSA. Each of three comparative studies showed non-inferiority of linezolid to vancomycin in the treatment of VAP [83–85]. A summary study combining the patients enrolled in two of the three trials significantly favoured linezolid in the Gram-positive and MRSA subsets. Logistic regression showed that linezolid was an independent predictor of survival, with ORs of 1.6 for all patients, 2.6 for Gram-positive VAP, and 4.6 for MRSA VAP [86].

In hospitalized patients with community-acquired pneumonia (CAP), empirical linezolid was more effective than ceftriaxone/cefpodoxime, with comparable cure rates in *Steptococcus pneumoniae* pneumonia and higher cure rates in pneumonia complicated by bacteraemia [87]. Linezolid could also be considered an alternative to vancomycin for treating serious infections caused by antimicrobial-resistant Gram-positive cocci in children [88].

Linezolid has also been approved for the treatment of complicated SSTIs (cSSTIs). In a randomized, double-blind, multicentre trial, linezolid was compared to oxacillin–dicloxacillin in patients with cSSTIs. The clinical cure rates were 69.8% and 64.9%, and the microbiological cure rates were 88.1% and 86.1%, in the linezolid and oxacillin–dicloxacillin groups, respectively. No serious drug-related adverse events were reported in the linezolid group [89]. In MRSA cSSTI infections, treatment with linezolid permits an earlier hospital discharge than treatment with vancomycin [90,91].

A study comparing the empirical use of linezolid and comparators for the treatment of patients suspected of CR-BSIs reported a higher mortality rate in the linezolid arm, due to Gram-negative superinfections. However, in patients with documented Gram-positive infections, linezolid was not inferior to comparators. This study [92] indicates that in patients with suspected CR-BSIs, empirical coverage against Gram-negative bacteria is always important until microbiological reports permit specific pathogen-directed therapy.

Linezolid is being used in other clinical situations in which further clinical trials are required to clarify its role.

Linezolid is a potentially useful drug for the treatment of patients with bone and joint infections due to MRSA. Adverse events associated with long-term use, such as bone marrow suppression and peripheral neuropathy, are the main issue [93–106].

Linezolid has been used successfully in the treatment of many cases of IE caused by resistant Gram-positive cocci. However, the studies are largely case reports, and many cases were failing with other drugs or were cases in which linezolid was introduced sequentially after other primary therapy. The use of a bacteriostatic antimicrobial for treatment of IE remains contrary to classic principles [81,107,108].

Linezolid has been used occasionally for the treatment of central nervous system infections, including meningitis and brain abscesses. In animal experimental models, the drug has shown good intraspinal cerebrospinal fluid (CSF) penetration. Linezolid has been used successfully as salvage therapy in cases of bacterial meningitis [109–118], ventriculitis [119–122], and even brain abscess [123].

Overall, linezolid is, at least, not inferior to vancomycin for the treatment of MRSA infections [49].

Co-trimoxazole

The potential role of folate antagonists, including trimethoprim–sulphamethoxazole, in the treatment of MRSA infections has been recently reviewed by Proctor *et al.* [124] and Grim *et al.* [125]. Sulfonamides are bacteriostatic against *S. aureus* by inhibiting dihydropteroate synthase and blocking folate biosynthesis. A second step in the inhibition of folate biosynthesis is carried out by trimethoprim, a tetrahydrofolate reductase inhibitor. The availability of exogenous thymidine may inactivate trimethoprim–sulphamethoxazole, as it bypasses the double biosynthetic blockade.

A high proportion of MRSA isolates susceptible to trimethoprim–sulphamethoxazole has been recently reported in different settings [126–128]. In the last nationwide study of *S. aureus* strains isolated in Spain, trimethoprim–sulphamethoxazole was active *in vitro* against almost 98% of all MRSA isolates [129,130].

Data on the treatment of MRSA with trimethoprim–sulphamethoxazole in animal models are contradictory, and the results may depend on the moment at which treatment is instituted and the liberation of thymidine from necrotic tissues [131].

The role of trimethoprim–sulphamethoxazole in the treatment of MRSA infections has been reviewed by Grim *et al.* [125]. In a randomized, prospective trial comparing trimethoprim–sulphamethoxazole with vancomycin [132] in intravenous drug users with endovascular infections caused by MSSA or MRSA (47% MRSA), trimethoprim–sulphamethoxazole was inferior to vancomycin in terms of duration of bacteraemia (6.7 vs. 4.3 days), sterilization of wound cultures (5.8 vs. 3.8 days), duration of fever, and failure rates (6/43 with trimethoprim–sulphamethoxazole vs. 1/58 with vancomycin).

For SSTIs, treatment with trimethoprim–sulphamethoxazole was compared with treatment with doxycycline in an area of high prevalence of MRSA. The overall clinical failure rate was 9%, with all failures occurring in the trimethoprim–sulphamethoxazole group [133].

The incidence of nosocomial pneumonia may be decreased by the prophylactic use of trimethoprim–sulphamethoxazole [134].

The value of adding rifampin to trimethoprim–sulphamethoxazole requires further investigation.

Trimethoprim–sulphamethoxazole, in summary, is a second-line agent for the treatment of severe MRSA infections in patients unable to receive more active drugs, such as glycopeptides or linezolid. If trimethoprim–sulphamethoxazole is selected, intravascular infections, and infections with abscesses or a high degree of necrotic tissue, must be avoided. Infections with low bacterial burden, as is the case in chronic osteomyelitis, and with no risk of death in case of clinical failure are better candidates for trimethoprim–sulphamethoxazole treatment [135].

Fusidic acid

Fusidic acid is derived from the fungus *Fusidium coccineum*, and was released for clinical use in the 1960s. The drug is available, at least in Europe and Australia, but not in the USA. Fusidic acid as an alternative for the treatment of MRSA has been extensively reviewed by Howden and Grayson [136].

Fusidic acid remains active *in vitro* against many strains of MSSA and MRSA, including hetero-VISA and VISA strains [137–139]. Between 1999 and 2005, more than 95% of 240 MRSA isolates in a Canadian hospital were susceptible to fusidic acid [139,140]. Resistance is generally defined as an MIC of $\geq$2 mg/L or as a zone (for a 2.5-μg disk) $\geq$22 mm. The prevalence of resistance of *S. aureus* to fusidic acid worldwide is highly variable, but overall is close to 5% [141]. In countries with higher rates, the spread of one or a few clones is usually responsible.

Fusidic acid inhibits the polypeptide elongation stage of bacterial protein synthesis. It is bacteriostatic at low concentrations and potentially bactericidal at higher concentrations [142].

The combination of fusidic acid with rifampin or β-lactams may be synergistic in certain circumstances, and this appears

to be associated with lower rates of development of fusidic acid resistance [138,143,144].

Fusidic acid is available in intravenous, oral and topical preparations, and has good tissue distribution, including bone, prostate, and abscesses [145,146].

Owing to good oral absorption, fusidic acid may be particularly useful for the ambulatory treatment of MRSA infections for which there are no better oral alternatives, such as trimethoprim-sulfamethoxazole or linezolid. It is frequently used in combination with rifampicin for long-term treatment of skin, soft tissue or osteoarticular infections due to MRSA after initial in-hospital treatment with other agents [147–150]. Clinical data to support the use of fusidic acid in combination with other β-lactams or glycopeptides for the treatment of staphylococcal bacteraemia, endocarditis and osteomyelitis are very limited [148,151]. The drug can be used topically for the treatment of acute skin infections and for decontamination in patients colonized with MRSA [152], particularly in settings in which mupirocin-resistant strains are prevalent. Topical therapy, however, has been associated with rapid emergence of resistance [153,154].

The main drawback of fusidic acid therapy is the development of resistance in 5–15% courses of treatment when the drug is used in monotherapy, and in much higher proportions after topical use. The development of resistance is significantly lower when the drug is used in combination with other agents [155,156].

The main side effects of fusidic acid are gastrointestinal tract discomfort, diarrhoea, and headache. Hepatotoxicity has been reported, and jaundice is a common manifestation. Jaundice is reversible and mainly associated with intravenous administration. Rarely reported side effects include granulocytopenia, thrombocytopenia, and venous spasm [157–159].

Fosfomycin

Fosfomycin is a phosphonic acid derivative produced by *Streptomyces* species, described in 1969 [160], that has been used in countries such as Japan, Spain, Germany and France for many years. Fosfomycin has an epoxide structure and a low molecular weight, and acts in the first stage of peptidoglycan synthesis of the bacterial wall. It has a rapid bactericidal effect and a wide spectrum of activity, including many MRSA strains [161–164]. Over the years, it has maintained its activity and has shown stable rates of resistance. It can be administered in combination (without antagonism) with glycopeptides, linezolid, quinupristin–dalfopristin, β-lactams, aminoglycosides, ansamycines, nitroimidazoles, and quinolones. A tromethamine derivative can be administered as an oral drug to treat urinary tract infections caused by some Gram-negative rods and *Enterococcus faecalis* [161,165–170]. A review of the subject has been recently published [171].

Intravenous fosfomycin has a relatively long half-life and achieves good penetration in inflamed tissues, including the aqueous and vitreous humor and the CSF. Fosfomycin does not bind to plasma proteins and is distributed widely, reaching high concentrations in interstitial fluid and tissues. It is renally excreted in its active form without metabolites and is dialysable.

Fosfomycin has a low rate of adverse events, which include mild gastrointestinal disturbances, phlebitis, and pain at the injection site.

The most common infections caused by *S. aureus* and treated with fosfomycin include meningitis, endophthalmitis, postoperative infections, pneumonia, septicaemia, endocarditis, and a miscellany of other infections. Unfortunately, clinical information regarding the use of fosfomycin in MRSA infections is very limited and is inadequate in several ways: studies are retrospective, the number of reported cases is small, and fosfomycin is frequently used in association with a second antibacterial agent, such as an aminoglycoside, a penicillin, or a cephalosporin [161,172–174].

Combinations of fosfomycin with β-lactam drugs, arbekacin and other drugs have shown *in vitro* and *in vivo* synergy against MRSA and are combinations that deserve trials [175–179]. The main drawback of fosfomycin is the rapid development of drug resistance.

Chloramphenicol

A very high proportion of MRSA isolates in different areas of the world remain susceptible to chloramphenicol, including community-acquired isolates [54,126,180–182]. In six sequential multicentre national studies of *Staphylococcus* performed in Spain from 1986 to 2006, the rates of chloramphenicol susceptibility ranged from 92% to 98% [129]. In the SENTRY study, 82% of MRSA isolates from patients with pneumonia were chloramphenicol-susceptible [183].

Unfortunately, the myelotoxicity of chloramphenicol and the absence of recent reported clinical experience with it in the treatment of MRSA infections limit its use to situations in which no better alternatives are available. Chloramphenicol in association with vancomycin has shown an antagonistic effect *in vitro* [184].

Synercid

Synercid is a streptogramin antimicrobial resulting from the combination of semisynthetic pristinamycin derivatives, quinupristin and dalfopristin, in a 3 : 7 ratio. The combination inhibits bacterial protein synthesis at different regions of the 50S ribosomal subunit [185]. It targets both early and late

stages of protein synthesis, resulting in synergistic activity [186]. Synercid is active *in vitro* against a high proportion of MRSA strains [187–190].

Synercid can be administered only intravenously, in a dextrose solution, and is eliminated mainly through bile into faeces. Clearance may be slightly impaired in patients with renal insufficiency.

Synercid inhibits the activity of the cytochrome P450 3A4 isoenzyme, which implies the existence of drug interactions, especially with cyclosporine. Synercid, by interfering with the metabolism of other drugs, may induce QTc prolongation [191,192].

Arthralgia and myalgia are the main adverse effects of synercid, and hyperbilirubinaemia and liver toxicity may occur. Pain and inflammation at the infusion site occur in up to 74% of patients [191,193,194].

Synercid gave worse clinical results in a rabbit model of MRSA arthritis than vancomycin alone or vancomycin plus rifampin [195]. Synercid was equivalent to other agents for the treatment of SSTIs, but was inferior to comparators for the treatment of pneumonia and IE [193,196].

Synercid has not gained regulatory approval by the FDA for the treatment of MRSA infections. The broad spectrum of adverse effects with synercid makes it an inferior choice for the treatment of MRSA infections.

New Glycolipopetides

Daptomycin

Daptomycin is a cyclic lipopeptide in clinical use and approved for the treatment of complicated skin and skin structure infections and right-sided endocarditis. The drug was developed in the early 1980s, but was initially abandoned because of concerns abouty skeletal muscle toxicity [197–200].

Daptomycin is active *in vitro* against staphylococci, including MRSA strains, and other Gram-positive bacteria [201–208].

Daptomycin causes a calcium-dependent rupture of the bacterial cell membrane, resulting in a net efflux of potassium that inhibits DNA, RNA, and protein synthesis. Unlike agents that are active against the cell wall, daptomycin has rapid bactericidal activity without cell lysis, a feature that could reduce the release of bacterial molecules and lessen the inflammatory response [209–211]. Daptomycin is available only for intravenous administration and is highly protein-bound (92%), with a half-life of approximately 8 h, allowing once-daily dosing.

Daptomycin does not require dose adjustments in patients with liver failure, but requires reduction in patients with renal failure, and complementary dosing after haemodialysis, because 15% of the drug is cleared after a 4-h dialysis session [212–214].

The daily dose for adults with normal renal function is 4 mg/kg, administered once daily for SSTIs, and no less than 6–10 mg/kg for cases of bacteraemia and endocarditis.

Daptomycin is approved by the FDA for the treatment of SSTIs caused by Gram-positive bacteria, including MRSA. Its efficacy is comparable to that of standard therapies [215–221].

Daptomycin has been prospectively compared with standard therapy in patients with *S. aureus* bacteraemia and/or right-sided endocarditis. Overall, 124 patients received 6 mg/kg daptomycin per day, and 122 received either an antistaphylococcal penicillin or vancomycin plus gentamicin. A successful outcome was documented for 53 of 120 patients who received daptomycin, as compared with 48 of 115 patients who received standard therapy, meeting the prespecified criteria for the non-inferiority of daptomycin. The success rates were similar in patients with MRSA isolates. Daptomycin, however, was associated with a higher rate of microbiological failure than was standard therapy (19 vs. 11 patients, p 0.17). Some isolates from patients with microbiological failure developed reduced susceptibility to daptomycin. Renal dysfunction occurred more frequently in the patients receiving vancomycin than in those receiving daptomycin (26% vs. 11%) [222].

Daptomycin has been successfully used for the treatment of bone [223–229] and joint [230] infections, but randomized comparative trials have not been published. In a small group of patients, decreased susceptibility to daptomycin occurred during the treatment of bone infections [227].

Daptomycin should not be used in patients with pneumonia, because of lack of efficacy due to the inactivation of daptomycin [231] by lung surfactant.

Resistance to daptomycin is uncommon but can be induced by serial passage in increasing concentrations of the antimicrobial [232]. Clinically, it has occurred in patients who have received prolonged treatment [233,234].

Data regarding central nervous system infections are very limited (the drug has poor activity), and daptomycin is not approved for this indication. *In vitro* activity against *Listeria monocytogenes* is very limited [235]. Cottagnound *et al.* [236] successfully treated pneumococcal meningitis with daptomycin. In a rabbit meningitis model, daptomycin displayed bactericidal activity significantly superior to vancomycin in the treatment of *S. aureus* infection. When it was given at a dose of 6 mg/kg, the penetration of daptomycin into inflamed meninges was 5%; daptomycin was therefore significantly more effective than vancomycin in sterilizing CSF. The level of penetration in non-inflamed meninges was 2% [237]. At

the present time, Daptomycin is not a potential alternative for the treatment of MRSA meningitis in patients who are not able to tolerate vancomycin.

Dalbavancin

Dalbavancin is a second-generation lipoglycopeptide with unique pharmacokinetic properties that allow dosing once weekly [238–240]. Dalbavancin has excellent activity against MRSA but not against vancomycin-resistant enterococci [241]. The drug inhibits bacterial cell wall formation by two different mechanisms. The dosage of dalbavancin is 1000 mg, intravenously initially, and 500 mg 7 days later.

The main clinical study with dalbavancin is an open study on CR-BSIs caused by MSSA, MRSA and coagulase-negative staphylococci. Infected patients who received weekly dalbavancin had an overall success rate that was significantly higher than that of those who received vancomycin. Adverse events and laboratory abnormalities were generally mild and comparable for the two drugs [242].

Clinical trials in cSSTIs suggest that dalbavancin is as effective as linezolid. Dalbavancin appears to be a promising new antimicrobial for the treatment of cSSTIs but FDA approval has been delayed [243,244].

Efficacy data for other types of infection, including pneumonia, bone and joint infections, bacteraemia, and endocarditis, are clearly needed.

Telavancin

Telavancin is another lipoglycopeptide that has a double mechanism of action. First, it inhibits peptidoglycan chain formation, blocking both transglycosylation and transpeptidation. Second, telavancin alters membrane potential and increases cellular permeability [245,246].

Telavancin is active *in vitro* against MRSA, including glycopeptide-intermediate *S. aureus* strains, and against the most important Gram-positive bacteria, including VanA-type *Enterococcus*. The drug has a high proportion of protein binding (93%), a high volume of tissue distribution, and a half-life of 7–9 h [247].

Clinically, telavancin has been studied in SSTIs, with results similar to those of comparators. In a randomized, double-blind, phase II trial, intravenous telavancin at 10 mg/kg every 24 h was compared with standard therapy (antistaphylococcal penicillin or vancomycin). Clinical success rates were similar in all populations. Among patients with MRSA at baseline (n = 45), clinical cure rates were 96% for telavancin and 90% for standard therapy. Microbiological eradication was significantly better with telavancin than with standard therapy, in particular in patients with MRSA (92% vs. 68%, p 0.04). The incidence and severity of adverse events and laboratory abnormalities were similar between the two groups [248,249].

The *in vitro* activity of telavancin is not affected by pulmonary surfactant [250], and phase III clinical trials in nosocomial pneumonia have been completed. The ATTAIN 1 and ATTAIN 2 studies are comparisons of telavancin and vancomycin for hospital-acquired pneumonia due to MRSA, but Telavancin is not yet FDA approved for the treatment of Nosocomial Pneumonia. [250]. A phase II, randomized, double-blind, parallel-group, multinational trial of intravenous telavancin for the treatment of uncomplicated *S. aureus* bacteraemia has also been completed.

Oritavancin

Oritavancin is another second-generation glycopeptide undergoing phase III clinical trials. It inhibits peptidoglycan biosynthesis at the same site as vancomycin (transglycosylation), but also forms dimers with higher affinity and at lower concentrations than vancomycin. The drug may also act as an inhibitor of the transglycosylase enzyme [252].

Oritavancin has a spectrum of *in vitro* activity similar to that of vancomycin, but is active against VanA, VanB and VanC *Enterococcus* and is fully active against MRSA, including some VRSA strains [253].

Oritavancin is available for intravenous administration and, with no detectable metabolism, is excreted slowly and unchanged in urine and faeces. It accumulates in tissues and macrophages, and has a very long terminal half-life that permits once-daily dosing [254,255]. The drug accumulates in the lysosomes and is slowly liberated from them [255]. The clinical importance of this effect needs further assessment.

In animal models, oritavancin has shown at least no inferiority to comparators in central venous catheter infections in rats, in a rabbit model of MRSA endocarditis, in a neutropenic mouse model, and in a thigh infection model [256].

Clinical trials comparing oritavancin with vancomycin for 3–7 days for the treatment of cSSTIs (the ARRI and ARRD studies) have shown no inferiority of oritavancin. Adverse events in these studies had the same or a better profile than the comparators. Oritavancin has fewer cutaneous adverse effects than vancomycin, the same nephrotoxicity as vancomycin, no ototoxicity, and no QTc alterations.

Oritavancin has also been studied in patients with *S. aureus* bacteraemia, excluding IE. Oritavancin once daily (5–10 mg/kg) was compared with vancomycin or a β-lactam antimicrobial for 10–14 days. Oritavancin was as effective as the comparators, but had greater clinical and microbiological success in doses of 10 mg/kg per day. Oritavancin is not yet FDA approved.

There is partial inhibition of oritavancin by surfactant, with mild to moderate reduction of potency; this effect is much less than that with daptomycin.

There is no need for oritanvancin dosage adjustment in renal insufficiency or moderate hepatic insufficiency.

Tigecycline

Tigecycline is a new broad-spectrum tetracycline derivative (glycylcycline) approved by the FDA in 2005. This drug is a tetracycline analogue and the first glycylcycline released for clinical use.

The glycylcyclines are being developed to overcome bacterial mechanisms of tetracycline resistance, such as ribosomal protection and efflux pumps. This drug binds to the 30S ribosomal subunit and blocks entry of amino-acyl tRNA into the A site of the ribosome. Tigecycline binds five times more efficiently to this ribosomal site than do tetracyclines [257,258].

Tigecycline has potent *in vitro* activity against a wide range of Gram-positive and Gram-negative bacteria, including MRSA and methicillin-resistant *Staphylococcus epidermidis* [259–268].

Tigecycline can be administered only by the parenteral route, initially in a single dose of 100 mg, and then in doses of 50 mg every 12 h. Moderate hepatic impairment reduces systemic clearance and prolongs the elimination half-life. Serum concentrations are low, but the penetration of the drug into skin blister fluid, bile, gall bladder, colon, and alveolar macrophages achieves concentrations greater than serum concentrations [269–273]. Levels in bone and synovial fluid are lower than concomitant serum concentrations [268,273,274]. Levels in the CSF with non-inflamed meninges vary between 5.5% and 41% of concurrent serum concentrations [273]. Biliary excretion is the primary route of elimination, and renal elimination accounts for 10–15% of the administered drug. Tigecycline does not need reduction in dosage in patients with renal failure, and is not dialysable. Tigecycline does not affect the cytochrome P450 enzymes, including CYP1A2, 2C8, 2C19, 2D6, and 3A4 [271,275–279].

Tigecycline has proven non-inferiority as compared with vancomycin plus aztreonam in the treatment of SSTIs [280,281], but patients with necrotizing fasciitis, osteomyelitis, neutropenia, gangrene, or impaired arterial blood supply were excluded. Eradication rates for MRSA isolates were similar between tigecycline and vancomycin–aztreonam. Gastrointestinal adverse events with tigecycline included nausea, vomiting, and diarrhoea. There were prolongations of activated partial thromboplastin time and prothrombin time in more patients treated with tigecycline than in those treated with vancomycin–aztreonam. MRSA was isolated from 65 patients, and treatment success rates were equivalent between the treatment groups.

Tigecycline is FDA-approved for the treatment of SSII and also for the treatment of complicated intra-abdominal infections. A pooled analysis of two international, multicentre, non-inferiority phase III trials showed that it is not inferior to imipenem–cilastatin in the treatment of intra-abdominal infections [282–285], but very few patients with MRSA infections were included in these studies.

The main issue regarding the role of tigecycline in the treatment of MRSA infections is its effectiveness in the treatment of other severe infections, including nosocomial pneumonia, bacteraemia, CR-BSIs, and bone and joint infections [286,287]. A study comparing tigecycline with imipenem–cilastatin in the treatment of nosocomial pneumonia ended recently, but full information is not yet available.

In a rat model of MRSA osteomyelitis, tigecycline was compared with teicoplanin and placebo. Both reduced the bacterial growth when compared with placebo [288].

Tigecycline was compared with vancomycin, with or without rifampicin, in a rabbit model of MRSA osteomyelitis. Rabbits that received tigecycline and oral rifampicin (n = 14) showed 100% infection cure; there was 90% clearance when tigecycline was used alone. Untreated controls (n = 15) demonstrated only 26% clearance [289]. Clinical data regarding efficacy of Tigecycline in human bone and joint infections are clearly needed.

Gastrointestinal effects have been reported with tigecycline. They include nausea, vomiting and diarrhoea, which usually occur during the first or second day of treatment, and are generally classified as mild to moderate, not requiring drug withdrawal.

Tigecycline undergoes minimal hepatic metabolism, and thus appears to have a low potential for drug–drug interactions.

Like tetracycline, tigecycline is a pregnancy category D drug. Because it is structurally related to the tetracyclines, it is considered to have similar safety concerns, such as pancreatitis, pseudotumour cerebri, anti-anabolic action, and photosensitivity. The use of tigecycline in patients less than 18 years of age is not recommended.

Tigecycline may be considered as alternative empirical therapy for patients with mild to moderate cSSTIs or Complicated Intra Abdominal infections. It may also be used as an alternative agent for patients who are allergic to vancomycin or those with significant renal impairment who have MRSA infections.

Anti-MRSA β-Lactam Drugs

Ceftobiprole

The classic concept that an MRSA isolate was an isolate with cross-resistance to all other β-lactam drugs is no longer true. Several new β-lactam agents are undergoing clinical trials, and will soon be added to the therapeutic armamentarium for MRSA infections.

Ceftobiprole is a new cephalosporin administered intravenously, with broad-spectrum *in vitro* activity. It is characterized by a strong affinity for penicillin-binding protein (PBP)2a and PBP2x, which are responsible for resistance in *Staphylococcus* spp. and *Streptococcus pneumoniae*, respectively. It is active against Gram-negative bacteria, including a high proportion of *Pseudomonas aeruginosa* strains, and against Gram-positive bacteria, including MRSA [290–292]. Ceftobiprole activity against MRSA includes both community and nosocomially acquired isolates [293–295].

Ceftobiprole medocaril administered intravenously is converted almost completely to the active drug, ceftobiprole. Ceftobiprole binds minimally (16%) to plasma proteins, undergoes minimal hepatic metabolism, and is rapidly eliminated, primarily unchanged, by renal excretion. The terminal elimination half-life is 3 h, and the predominant mechanism responsible for elimination is glomerular filtration. Ceftobiprole does not significantly induce or inhibit relevant cytochrome P450 enzymes, and is neither a substrate for nor an inhibitor of P-glycoprotein. The pharmacokinetics of ceftobiprole are linear following single and multiple infusions of 125–1000 mg [292,296,297].

In patients with moderate to severe renal impairment, dose adjustments for the treatment of infections caused by target pathogens, including MRSA, should be based on creatinine clearance [296].

In a multicentre, multinational, double-blind, randomized trial concerning treatment of cSSTIs caused by Gram-positive bacteria, ceftobiprole (500 mg every 12 h) was compared with vancomycin (1 g every 12 h). Overall, 93% of those treated with ceftobiprole and 93% of those treated with vancomycin were cured. The cure rates for patients with MRSA infections were 91.8% (56/61) with ceftobiprole treatment and 90.0% (54/60) with vancomycin treatment. Only 4% of patients treated with ceftobiprole required drug discontinuation because of adverse events [298].

Ceftobiprole is undergoing clinical evaluation in animal models of respiratory tract infection [299] and in human trials. A study comparing ceftobiprole with ceftriaxone in patients with CAP has been completed. Two phase III trials concerning nosocomial pneumonia have been completed. They included both patients with VAP and non-VAP cases. The results were not uniform in both groups, or in all age strata, but final reports are pending.

A trial assessing the role of ceftobiprole in the treatment of hospitalized patients with *S. aureus* bacteraemia was withdrawn prior to recruitment.

A study of the effectiveness of ceftobiprole treatment of patients with fever and neutropenia has been suspended because of the FDA medwatch on the comparator drug, cefepime.

Ceftaroline

Ceftaroline is a novel cephalosporin with broad-spectrum activity against Gram-negative and Gram-positive pathogens. The antimicrobial activity of ceftaroline is similar to that of ceftriaxone, with one major difference: ceftaroline is also very potent against MRSA [300–302].

A randomized, observer-blinded study to evaluate the safety and efficacy of ceftaroline vs. standard therapy in adult patients with complicated skin and skin structure infections showed a clinical cure rate of 96.7% (59/61) for ceftaroline vs. 88.9% (24/27) for standard therapy. The microbiological success rate was 95.2% (40/42) for ceftaroline vs. 85.7% (18/21) for standard therapy. Most adverse events resulting from ceftaroline were mild and not related to treatment [303].

Using the rabbit endocarditis model, ceftaroline was compared with linezolid and vancomycin against MRSA. After a 4-day treatment, ceftaroline exhibited superior bactericidal *in vivo* activity against MRSA strains, and appeared to be the most effective drug against a heterogeneous glycopeptide-intermediate *S. aureus* strain [304].

Currently, ceftaroline is being compared with ceftriaxone in two clinical trials involving adults with CAP.

Carbemenems

Carbamenems may also impact on the treatment of MRSA infections. Tomopenem (formerly CS-023) is a novel 1β-methylcarbapenem with a broad-spectrum coverage of Gram-positive and Gram-negative pathogens. The MICs of tomopenem for MRSA and *P. aeruginosa* at which 90% of the isolates tested were inhibited were 8 and 4 mg/L, respectively, and were ≥four-fold lower than those of imipenem and meropenem. The antibacterial activity of tomopenem against MRSA was correlated with a higher affinity for PBP2a [305].

Other Potential New Drugs

Iclaprim (formerly AR-100, Ro 48-2622) is a diaminopyrimidine dihydrofolate reductase inhibitor [306–309]. This compound is active against Gram-positive bacteria, including

Enterococcus spp. and MRSA, VISA, VRSA and macrolide-resistant, quinolone-resistant, and trimethoprim-resistant strains. In addition, iclaprim has demonstrated activity against *Streptococcus pneumoniae*, including penicillin-resistant, erythromycin-resistant, levofloxacin-resistant, and trimethoprim–sulphamethoxazole-resistant strains. Furthermore, it has *in vitro* activity against Gram-negative bacteria and atypical bacteria [310,311].

Iclaprim is highly synergistic with sulphamethoxazole and sulphadiazine, and is neither synergistic nor antagonistic with macrolides, lincosamides, aminoglycosides, quinolones, β-lactams, trimethoprim, tetracyclines, and glycopeptides [312].

Iclaprim is available for intravenous and oral use, with very good oral bioavailability. Oral iclaprim undergoes rapid absorption and is subject to presystemic metabolism. Both intravenous and orally administered iclaprim undergo complete biotransformation, and the excretion of metabolites is predominantly in the urine (Brandt *et al.*, 47th ICAAC, 2007, Abstract A–804).

Phase II clinical trials have shown promise for use in cSSTIs that are caused by MRSA, and two phase III clinical trials have been recently completed for the same indication.

Two studies of iclaprim in cSSTIs have been completed. The ASSIST-1 trial was a phase 3 safety and efficacy study of intravenous iclaprim vs. linezolid in cSSTI. The ASSIST-2 study evaluated intravenous iclaprim vs. linezolid in cSSTIs.

Iclaprim successfully met its primary endpoints, namely non-inferiority in clinical cure rates vs. linezolid and vancomycin. Iclaprim is not FDA approved at the time of writing (November 2009).

Currently, iclaprim is undergoing clinical trials concerning hospital-acquired VAP and other forms of nosocomial pneumonia.

Tefibazumab (Aurexis) is a humanized monoclonal antibody that binds to the surface-expressed adhesion protein clumping factor A [313]. It is under development as adjunctive therapy for serious *S. aureus* infections, but additional trials are warranted to address the dosing range and efficacy of tefibazumab [315].

Transparency Declaration

E. Bonza has advised or received payment for conferences from Pfizer, Novartis, MSD, Cerexa, Astellas and Optimer.

References

Available as supporting information online.